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Epidemiology of colorectal polyps

Abstract The prevalence of colorectal adenomatous polyps varies widely from country to country. Among asymptomatic, average-risk patients, adenoma prevalence averages approximately 10% in sigmoidoscopy studies and more than 25% in colonoscopy studies, whereas the prevalence of colorectal cancer among these patients is less than 1%. These data may change in the future due to the advent of new technological approaches and, in particular, chromo- and magnifying endoscopy as well as confocal laser endoscopy. The cumulative incidence of new adenomas within 3 years after normal endoscopy averages about 7% by flexible sigmoidoscopy and 27% by colonoscopy. As far as risk factors for colorectal adenomas are concerned, several data are now available on the potential role of various diet items. Tobacco smoking may be important in the early stages of adenoma formation, but not necessarily in the later stages. Alcohol consumption elevates the risk of adenomatous colorectal polyps and this seems increased by ADH3 polymorphism. Another gene–environment relationship of interest in colorectal tumorigenesis may be based on folate's effects on K-ras mutations.

Key words Colon • Polyps • Epidemiology

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Introduction

The prevalence of colorectal adenomatous polyps varies widely from country to country and is highly correlated with colorectal cancer incidence rates in each country. The prevalence of adenomas reported in older studies was based on autopsy findings and is higher than that in more recent studies based on endoscopy findings. Among asymptomatic, average-risk patients, adenoma prevalence averages approximately 10% in sigmoidoscopy studies and more than 25% in colonoscopy studies, whereas the prevalence of colorectal cancer among these patients is less than 1%. The cumulative incidence of new adenomas within 3 years after normal endoscopy averages about 7% by flexible sigmoidoscopy and 27% by colonoscopy [1].

The prevalence of colorectal lesions in persons 40–49 years of age, as identified on colonoscopy, has been evaluated by Imperiale et al. [2], reviewing the procedure and pathology reports for 906 consecutive persons 40–49 years of age who voluntarily participated in an employer-based screening-colonoscopy programme. The histologic features of lesions that were identified and removed on endoscopy were categorised according to those of the most advanced lesion removed proximally (up to the junction of the splenic flexure and the descending colon) and the most advanced lesion removed distally. An advanced lesion was defined as an adenoma at least 1 cm in diameter, with histologic villous configuration, severe dysplasia or a cancer. Among those who underwent colonoscopic screening, 78.9% had no detected lesions, 10% had hyperplastic polyps, 8.7% had tubular adenomas and 3.5% had advanced neoplasms, none of which were cancerous [2]. Eighteen of 33 advanced neoplasms (55%) were located distally and were potentially within reach of a sigmoidoscope. If these results are applicable to the general population, at least 250 persons, and perhaps 1000 or more, would need to be screened to detect one cancer in this age group [2]. The low yield of screening

colonoscopy in this age group is consistent with current recommendations about the age at which to begin screening in persons at average risk.

Hyperplastic polyps

In 2003, Dave et al. [3] reviewed the literature regarding the association of distal hyperplastic polyps and synchronous neoplasia (adenomatous polyps and cancer) in the proximal colon.

Of 18 included studies, 12 involved asymptomatic individuals in which the pooled absolute risk of any proximal neoplasia associated with distal hyperplastic polyps was 25% [3]. In 4 studies where colonoscopy was performed irrespective of distal findings, the absolute risk was 21% (95% confidence interval (CI), 14–28%). The relative risk of finding any proximal neoplasia in persons with distal hyperplastic polyps was 1.3, compared to those with no distal polyps. Among 6 studies of patients with symptoms or risk factors for neoplasia, the absolute risk of proximal neoplasia was 35% in persons with distal hyperplastic polyps. In 2 studies of screening colonoscopy, advanced proximal neoplasia (cancer, or a polyp with villous histology or severe dysplasia, or a tubular adenoma ≥1 cm) was present in 4–5% of persons with distal hyperplastic polyps, which was 1.5–2.6 times greater than in those with no distal polyps. As a consequence, in asymptomatic persons, a distal hyperplastic polyp is associated with a 21–25% risk for any proximal neoplasia and a 4–5% risk of advanced proximal neoplasia, and may justify examination of the proximal colon [3].

Risk factors

Knowledge of risk factors for colorectal neoplasia could inform risk reduction strategies for asymptomatic individuals. Few studies have evaluated risk factors for advanced colorectal neoplasia in asymptomatic individuals, compared risk factors between persons with and without polyps, or included the most purported risk factors in a multivariate analysis (Table 1). A prospective, cross-sectional study of 3121 asymptomatic patients aged 50–75 years has been conducted by Lieberman et al. [4]. All participants had complete colonoscopy to determine the prevalence of advanced neoplasia, defined as an adenoma that was 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia or invasive cancer. Variables examined included history of a first-degree relative with colorectal cancer, prior cholecystectomy, serum cholesterol level, physical activity, smoking, alcohol use and dietary factors. Three hundred and twenty-nine participants had advanced neoplasia and 1441 had no polyps. In multivariate analyses, positive associations for history of a first-degree relative with colorectal cancer (odds ratio (OR), 1.66; 95% CI, 1.16–2.35), current smoking (OR, 1.85; 95% CI, 1.33–2.58) and current moderate to heavy alcohol use (OR, 1.02; 95% CI, 1.01–1.03) were found. Inverse associations were found for cereal fibre intake (OR, 0.95; 95% CI, 0.91–0.99), vitamin D intake (OR, 0.94; 95% CI, 0.90–0.99) and use of nonsteroidal anti-inflammatory drugs (NSAIDs) (OR, 0.66; 95% CI, 0.48–0.91) [4]. In the univariate analysis, the inverse association was found with cereal fibre intake greater than 4.2 g/day, vitamin D intake greater than 645 IU/day and daily use of NSAIDs. Marginal factors included physical activity, daily multivitamin use, and intake of calcium and fat derived from red meat. No association was found for body mass index, prior cholecystectomy or serum cholesterol level. Three hundred and ninety-one patients had hyperplastic polyps as the worst lesion found at colonoscopy. Risk variables were similar to those for patients with no polyps, except that past and current smoking was associated with an increased risk of hyperplastic polyps.

Table 1 Differences between risk factors for colorectal adenomas and carcinomas [13]

Risk factors	Adenomas	Carcinomas
Subsite distribution	Relatively uniform	Concentrated distally
Sex ratio (M/F)	1.5–2.0	About 1
Tromso (Norway) *vs*. Liverpool (UK)	Similar prevalence	2.5-fold range in risk
Iran *vs*. Colombia	Very different risk	Similar risk
Role of tobacco	Increased risk	No relation
Role of alcohol	Increased risk	No relation to colon cancer Rectal cancer ?
Role of vitamin E	Increased risk?	Decreased risk?

Alcohol

Alcohol is a probable risk factor with regard to colorectal neoplasm and is metabolised to the carcinogen acetaldehyde by the genetically polymorphic alcohol dehydrogenase 3 (ADH3) enzyme. Tiemersma et al. evaluated whether the association between alcohol and colorectal adenomas is modified by ADH3 polymorphism [5]. They recruited 433 cases with adenomatous polyps and 436 polyp-free controls among Caucasians undergoing endoscopy between 1995 and 2000.

Multivariate analyses adjusting for gender, age and indication for endoscopy showed that alcohol increased the

risk of colorectal adenomas among women [OR, 1.8; 95% CI, 1.0–3.2, ≥10 *vs*. <1 drink/week]. Among men, the risk of adenomas was increased only for those consuming >21 drinks/week (OR, 1.8; 95% CI, 0.9–3.8, compared with men drinking <1 drink/week). Among subjects in the highest tertile of alcohol consumption, those with the ADH3*1/*1 genotype were at higher risk (OR, 1.8; 95% CI, 1.0–3.1) than those with other ADH3 genotypes (OR, 1.2; 95% CI, 0.7–1.9) when compared with those in the lowest tertile with ADH3*1/*2 or ADH3*2/*2 genotypes [5]. These findings are consistent with results of other studies, suggesting that alcohol consumption elevates the risk of adenomatous colorectal polyps. ADH3 polymorphism may modify the association between alcohol consumption and colorectal adenomas.

Different risks for early and late stages of adenoma formation

Within a 3-year follow-up and intervention study with calcium and antioxidants against growth and recurrence of colorectal polyps, supplementary studies were performed in which different aspects of lifestyle were examined [6]. Instead of polypectomy at diagnosis, polyps <9 mm were left *in situ* in 116 polyp patients (50–76 years, 50% men). After 3 years, all polyps were removed and subjected to histology [6].

An increased adenoma risk compared with controls, related to a typically unhealthy diet with a high intake of fat and a low intake of fibre and antioxidants, was found. In this study it was also observed that tobacco smoking may be important in the early stages of neoplasia formation, but not necessarily in the later stages [6].

These data support the theory that different factors may be of importance in different stages of the neoplastic formation, and that lifestyle-related factors are likely to play a major role in CRC development.

Folate-metabolising gene polymorphism

The studies of Chen et al. on interactions of a folate-metabolising gene polymorphism and dietary intake in colorectal tumorigenesis demonstrate the potential importance of studying interactions between genotype and environmental exposure in relation to cancer risk [7]. They observed an inverse association of a polymorphism (667C→T, ala→val) in the methylenetetrahydrofolate reductase (MTHFR) gene with colorectal cancer but not with colorectal adenomas [7]. The inverse association of methionine and adverse association of alcohol with colorectal cancer were stronger among val/val individuals. These interactions were not present in studies of colorectal adenomas [7]. Therefore, studying gene–environment interactions in relation to cancer can be of importance in clarifying cancer aetiology as well as pointing to preventive dietary modifications.

K-ras protooncogene

The K-ras protooncogene is frequently mutated in colorectal adenocarcinomas, but the aetiology of this molecular event is uncertain. Martinez et al. [8] investigated the association between variables known or suspected to be related to risk for colorectal cancer and the occurrence of Ki-ras mutations in colorectal adenomas. This study was conducted among 678 male and female participants, 40–80 years of age, enrolled in a phase III trial testing the effects of a wheat bran fibre supplement on adenoma recurrence. Exposure information on the risk factors of interest was assessed through self-administered questionnaires. Mutations in codons 12 and 13 of the Ki-ras protooncogene were analysed in baseline adenomas 0.5 cm or larger by PCR amplification followed by direct sequencing. Eighteen per cent (120 of 678) of the participants had one or more adenoma(s) with Ki-ras mutations. A higher risk of Ki-ras mutations was associated with increasing age and a lower intake of total folate [8]. The OR for Ki-ras mutations for individuals >72 years of age was 1.98 [95% CI, 1.19–3.27; p for trend=0.008] compared with those less than 65 years of age. Compared with individuals in the lower tertile of total folate, those in the upper tertile had an approximately 50% lower risk of having Ki-ras mutation-positive adenomas (OR, 0.52; 95% CI, 0.30–0.88; p for trend=0.02) [8]. There was a suggestion of a stronger inverse association of total folate with G→T transversions (OR, 0.41; 95% CI, 0.20–0.87) than G→A transitions (OR, 0.61; 95% CI, 0.31–1.21), although the CIs for the associations overlap [8]. The results of these analyses suggest that the protective effect of folate in colon cancer observed in published studies may be mediated through folate's effect on Ki-ras mutations.

The follow-up of colorectal adenomas [9]

Removal of adenomas can reduce the incidence of colorectal cancer. This conclusion is based on observational data and comparison with historical controls and expected cancer rates. A randomised controlled study of polyp removal in adenoma patients is not ethically feasible. The finding of hyperplastic polyps in the rectosigmoid is not an indication for total colonoscopy. Follow-up colonoscopy of patients in whom an adenoma has been colonoscopically removed is recommended after 3 years, provided the initial colono-

scopic examination was technically satisfactory. In particular, patients at initial examination with multiple adenomas, adenomas of size >0.5 cm or with a family history of colorectal cancer should be followed after 3 years; those with a single tabular adenoma of size ≤0.5 cm and no family history can wait until 5 years for follow-up. If no further neoplasia is detected, then a 5-year interval is probably justified before the subsequent re-examination.

Chromo- and magnifying endoscopy

The goal of every routine endoscopy in the gut is the early diagnosis of malignant and premalignant changes of the mucosa. Chromo- and magnifying endoscopes are exciting new tools and offer detailed analysis of the colonic mucosal surface and pit pattern architecture, thus changing the current epidemiology of colorectal polyps.

Surface analysis of the colon using chromoendoscopy allows a prediction between non-neoplastic and neoplastic lesions with high specificity. The precise delineation of the borders and a more detailed macroscopic analysis of the lesions are further advantages. In particular, flat adenomas and early depressed cancers are now more frequently recognised in western countries, suggesting that significant lesions were overlooked by conventional endoscopy in the past. Furthermore, chromoendoscopy can be used in a targeted fashion to screen for sporadic adenomas. Finally, in surveillance colonoscopy, patients with long-standing ulcerative colitis have a valuable benefit if targeted biopsies are performed to detect intraepithelial neoplasias after pan-chromoendoscopy with methylene blue. Although there is a long learning curve, chromoendoscopy should thus belong to every endoscopist's armamentarium. However, detailed knowledge about the technique, dyes and specific staining patterns are mandatory before the yield of screening or surveillance colonoscopy can be increased. The new detailed images seen with magnifying chromoendoscopy are unequivocally the beginning of a new era where new optical developments will allow a unique view of cellular structures [10].

During routine colonoscopy, vital staining with indigocarmine solution (0.4%, 1–10 ml) was performed on all visible lesions in 100 consecutive patients without visible inflammatory changes by Kiesslich et al. [11]. If findings on macroscopic examination were unremarkable, the sigmoid colon and rectum were stained with indigocarmine over a defined segment (0–30 cm ab ano) and inspected for lesions visible only after staining. Each lesion was classified with regard to type (polypoid, flat or depressed), position and size. The staining pattern was classified according to the pit pattern classification. A total of 52 patients had 105 visible lesions (89 polypoid, 14 flat and two depressed) [11]. The mean size of the lesions was 1.4 cm. Among the 48 patients with mucosa of normal appearance, 27 showed 178 lesions after staining (176 flat, two depressed) with a mean size of 3 mm. On histological investigation, 210 lesions showed hyperplastic or inflammatory changes, 67 were adenomas and six were cancers. Use of the pit pattern system to classify lesions (adenomatous, pit patterns III–V; nonadenomatous, pit patterns I–II) was possible, with a sensitivity of 92% and a specificity of 93%. Lesions with pit patterns III–V showed higher rates of dysplasia.

Therefore, chromoendoscopy allows easy detection of mucosal lesions in the colon and facilitates visualisation of the margins of flat lesions. This technique unmasks multiple mucosal lesions that are not identified by routine video colonoscopy. The pit pattern seen after staining allows differentiation between hyperplastic and adenomatous lesions, which may have consequences with regard to the endoscopic interventions needed.

Confocal laser endoscopy

A confocal laser endoscopy system has recently been developed that may allow subsurface imaging of living cells in colonic tissue *in vivo*. In the experience of Kiesslich et al. [12] at the Johannes Gutenberg University of Mainz, 27 patients underwent colonoscopy with the confocal endoscope using acriflavine hydrochloride or fluorescein sodium with blue laser illumination. Furthermore, 42 patients underwent colonoscopy with this system using fluorescein sodium. Standardised locations and circumscript lesions were examined by confocal imaging before taking biopsy specimens. Confocal images were graded according to cellular and vascular changes and correlated with conventional histology in a prospective and blinded fashion. Acriflavine hydrochloride and fluorescein sodium both yielded high-quality images. Whereas acriflavine hydrochloride strongly labelled the superficial epithelial cells, fluorescein sodium offered deeper imaging into the lamina propria. Fluorescein sodium was thus used for the prospective component of the study in which 13 020 confocal images from 390 different locations were compared with histologic data from 1038 biopsy specimens. Subsurface analysis during confocal laser endoscopy allowed detailed analysis of cellular structures. The presence of neoplastic changes could be predicted with high accuracy (sensitivity, 97.4%; specificity, 99.4%; accuracy, 99.2%) [12].

According to this experience, confocal laser endoscopy is a novel diagnostic tool to analyse living cells during colonoscopy, thereby enabling virtual histology of neoplastic changes with high accuracy. These newly discovered diagnostic possibilities may be of crucial importance in clinical practice and lead to an optimised rapid diagnosis of neoplastic changes during ongoing colonoscopy.

References

1. Neugut AI, Jacobson JS, Rella VA (1997) Prevalence and incidence of colorectal adenomas and cancer in asymptomatic persons. Gastrointest Endosc Clin N Am 7:387–399
2. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF (2002) Results of screening colonoscopy among persons 40 to 49 years of age. N Engl J Med 346:1781–1785
3. Dave S, Hui S, Kroenke K, Imperiale TF (2003) Is the distal hyperplastic polyp a marker for proximal neoplasia? J Gen Intern Med 18:128–137
4. Lieberman DA, Prindiville S, Weiss DG, Willett W; VA Cooperative Study Group 380 (2003) Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 290:2959–2967
5. Tiemersma EW, Wark PA, Ocke MC, Bunschoten A, Otten MH, Kok FJ, Kampman E (2003) Alcohol consumption, alcohol dehydrogenase 3 polymorphism, and colorectal adenomas. Cancer Epidemiol Biomarkers Prev 12:419–425
6. Almendingen K, Hofstad B, Vatn MH (2002) Lifestyle-related factors and colorectal polyps: preliminary results from a Norwegian follow-up and intervention study. Eur J Cancer Prev 11:153–158
7. Chen J, Giovannucci EL, Hunter DJ (1999) MTHFR polymorphism, methyl-replete diets and the risk of colorectal carcinoma and adenoma among U.S. men and women: an example of gene–environment interactions in colorectal tumorigenesis. J Nutr 129[Suppl 2]:560–564
8. Martinez ME, Maltzman T, Marshall JR et al (1999) Risk factors for Ki-ras protooncogene mutation in sporadic colorectal adenomas. Cancer Res 59:5181–5185
9. Young GP, Rozen P, Levin B (eds) (1996) Prevention and early detection of colorectal cancer. WB Saunders, London, p 195
10. Kiesslich R, Jung M, DiSario JA, Galle PR, Neurath MF (2004) Perspectives of chromo and magnifying endoscopy: how, how much, when, and whom should we stain? J Clin Gastroenterol 38:7–13
11. Kiesslich R, von Bergh M, Hahn M, Hermann G, Jung M (2001) Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 33:1001–1006
12. Kiesslich R, Burg J, Vieth M et al (2004) Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. Gastroenterology 127:706–713
13. Hill MJ, Davies GJ, Giacosa A (2001) Should we change our dietary advice on cancer prevention? Eur J Cancer Prev 10:1–6